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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/251,570	02/17/99	WINKEL J	MXI-101

EXAMINER	
DECLOUX, A	

ART UNIT	PAPER NUMBER
1644	9

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HM12/0327

DATE MAILED: 03/27/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/251,570	Van De Winkel
Examiner	**Group Art Unit**
DeCloux, Amy	1644

☒ Responsive to communication(s) filed on *mailed on 1-2-01*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-21* is/are pending in the applicat

Of the above, claim(s) *7* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-6 and 8-21* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's amendment, mailed 1-2-01 (Paper No. 8), is acknowledged.

Claims 22-25 have been canceled. Claims 1-21 are currently pending. Claim 7 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim.

2. The rejections of record can be found in the previous Office Action mailed 6/30/00 (Paper No. 7). In view of applicant's amendment, mailed 1-2-01 (Paper No. 8), the objection, the 101 utility rejection and both 112 first rejections have been withdrawn. However, the art rejections are maintained.

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. By referring to page 40 of the instant specification, Applicant traverses the 112 first rejection on the grounds that they have provided written description and working examples for treating or prophylactically preventing disorders characterized by aberrant numbers or activity of macrophages, and for preventing or delaying the occurrence of the onset or recurrence of macrophage mediated disease state using the claimed method. While examiner agrees with the applicant that the specification is enabling for the treatment of said disorders, the specification is not enabling for preventing or prophylactically preventing said disorders because it provides insufficient guidance and direction exemplifying the prevention of a disease as recited in claim 2, especially since the specification provides insufficient guidance and direction that the singular cause of a disease (as opposed a characteristic feature of a disease) is due to aberrant numbers or activity of macrophages. Examiner agrees with applicant that Example 9 shows that repeated injections with the immunotoxin suppressed cutaneous inflammation for a prolonged period, however said example does not show evidence of preventing diseases. Therefore, though applicant's arguments have been carefully considered, they are not deemed persuasive, and the rejection which is repeated below for applicant's convenience is maintained.

Claims 2-6, 8-12 and 19-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn a method of preventing a disease in a subject characterized by aberrant activity or number of macrophages , comprising administering an agent that binds to an Fc receptor and kills or reduces the activity of macrophages. However, the specification does not enable one of skill in the art regarding the **prevention** of said disease, because the specification does not enable one of skill in the art regarding the efficacy of administering in vivo, the recited macrophage binding compound in said method of preventing a disease characterized by aberrant activity or number of macrophages. The efficacy of the claimed methods is not adequately taught by the specification because it does not teach how to extrapolate data obtained from experiments using the claimed methods to treat said diseases to the development of the claimed methods to prevent said diseases, especially in view of the large number of diseases encompassed by the recited claims which may have multiple causes or origins.

Based upon the paucity of additional information supportive of the recited methods in the prevention of said macrophage related diseases within the instant specification, it would require an undue amount of experimentation on the part of one skilled in the art to practice the claimed method

5. The following is a quotation of the appropriate paragraphs of *35 U.S.C. § 102* that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Regarding the 102 (a) rejection of claims 1-6, anticipated by Curnow, applicant traverses said rejection on the grounds that Curnow fails to teach any method of using mab H22 (ie MDX-33) to reduce the number or activity of macrophages as claimed by applicants, much less to treat or prevent macrophage mediated disorders. The examiner notes that the limitation of treatment or prevention of macrophage mediated disorders is not recited in claim 1. Furthermore, the examiner points out that Curnow teaches on page 213, column 2, second full paragraph, that monocytes and macrophages that express Fc receptors for IgG (FcgR) (CD64) play an important role in platelet destruction and that crosslinking CD64 by CD64 specific antibodies down modulates CD64 significantly and therefore said antibodies may be useful in treating the autoimmune disease of ITP. Since down modulating CD64 by CD64 specific antibodies reduces the activity of CD64 bearing cells such as macrophages, and since Graziano teaches that mabs 22 and 32 bind the FcγRI receptor with their Fv at sites that are distinct from the Fc binding site, the teachings of Curnow as evidenced by

Graziano anticipate the claimed invention. Therefore, though applicant's arguments have been considered carefully, they are not deemed persuasive, and the rejection which is repeated below for applicant's convenience, is maintained.

Claims 1-6 are rejected under 35 U.S.C. 102(a) as being anticipated by Curnow, R.T. (Cancer Immunol Immunother. 45:210-215, 1997), as evidenced by Graziano et al (J. Immunol. 155:4996-5002, 1995) .

Curnow, R.T. teaches that mabH22 (which they call MDX-33), binds circulating monocytes causing monocytopenia and down modulates CD64 (FcγRI) on monocytes, and that the activity of phagocytosis is fully inhibited for at least 6 days after invivo administration of mabH22 which indicates its importance in the treatment of autoimmune disorders, including ITP which is characterized by platelet destruction by CD64 bearing monocytes and macrophages which express FcγR (see entire article, especially page 210, column 1, lines 12-14, and column 2, lines 27-29, and page 211, column 1, lines 6-18 and page 213, column 2, second full paragraph).

Graziano et al teach that mabs 22 and 32 bind the FcγRI receptor (CD64) with their Fv at sites that are distinct from the Fc binding site, and that the humanization of monoclonal antibody 22 eliminates immunogenicity (see entire article including third paragraph of page 4996) and represents an important step in the development of anti-FcgRI-based molecules for the treatment of human diseases (see entire article including the last paragraph the article). The rejection is made on the basis that the mabH22 itself has the function of agents a) and b) recited in the claims.

Therefore, the reference teachings anticipate the claimed invention.

6. Regarding the 102 (b) rejection of claims 1-6 and 18, anticipated by Erickson et al, applicant traverses said rejection on the grounds that Erickson et al fails to teach or suggest a method of treating macrophage disorders as claimed by applicants. Examiner first notes that claim 1 is not drawn to a method of treating macrophage-mediated disorders, but recites a method of selectively reducing the number or activity of macrophages. Secondly, the examiner notes that Erickson teaches on page 719, column 1, first full paragraph, that down-modulation of FcγRI on macrophages which are known to be major effectors in platelet destruction in ITP, could result in reduced platelet destruction, and further notes that monocytes were chosen as a readily available representative of the reticuloendothelial system for studying the effect of monoclonal antibody 197 for down modulation of FcγRI.

Applicant further traverses said rejection on the grounds that the monoclonal antibody 197 employed by Erickson et al does not bind to an Fc receptor at a site which is distinct from that bound by endogenous immunoglobulin as required by claim 1 and its dependent claims. However, the examiner notes in the abstract, Erickson teaches that said monoclonal antibody has two distinct binding epitopes of FcγRI, one

epitope being a non-Fc binding domain of the receptor recognized by the variable region of said monoclonal antibody, said first epitope being distinct from a second epitope which is the Fc binding domain of the FcγRI, and therefore said antibody meets the claim limitation of claim 1 and dependent claims 2-6 and 18. Therefore, though applicant's arguments have been considered carefully, they are not deemed persuasive, and the rejection which is repeated below for applicant's convenience is maintained.

Claims 1-6 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Erickson et al (British Journal of Haematology, 92:718-724, 1996).

Erickson et al teach mab197 binds the FcγRI by its fab region to a nonligand binding domain of FcgRI as well as by its fc region and that it can effectively crosslink FcRγI on the surface of the human U-937 human monocyte-like cell line resulting in receptor activation and modulation and that down modulation of FcgRI on circulating monocytes occurs in vivo after infusion of murine mab 197 in ITP patients, (see entire article , especially page 722, second paragraph of the discussion, and last paragraph of page 723). Erickson et al also teaches ITP is characterized by destruction of immunoglobulin coated platelets by mononuclear phagocytes and that macrophages are thought to be the major effectors in platelet destruction in ITP, and that the patient showed major clinical improvement after the first mab infusion (see entire article especially page 718, first paragraph, page 719, first full paragraph, and page 722, column 2, third full paragraph). Therefore, the reference teachings anticipate the claimed invention.

Erickson et al also teach that treatment of the human monocyte cell line U-937 with mab 197 has been shown to result in rapid internalization of FcγR1(see entire article, including page 720, last paragraph of column 1) thus reducing the activity of the macrophages like cell line. The rejection is made on the basis that the mab197 itself has the function of agents a) and b) recited in the claims. Therefore, the reference teachings anticipate the claimed invention.

7. The following is a quotation of *35 U.S.C. § 103* which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made. Subject matter developed by another person, which qualifies as prior art only under *subsection (f) or (g)* of *section 102* of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

8. Regarding the 103 rejection over Curnow, R.T. (Cancer Immunol Immunother. 45:210-215, 1997), Graziano et al (J. Immunol. 155:4996-5002, 1995) and Erickson et al (British Journal of Haematology, 92:718-724, 1996), in view of Uhr et al (U.S. Patent No. 5686072) Ghetie et al (U.S. Patent No. 5578706), Rybak et al (U.S. Patent No. 5840840), Pastan et al (U.S. Patent 5489525), and Bjerke et al (ACTA Derm Venereol (Stockh) 1994; Suppl.186:141-142), appliacnt traverses the rejection on the grounds that none of the cited references either alone or in combination teach or suggest the treatment of macrophage-mediated disorders as claimed by applicants. In contradiction to said assertion, the examiner points out, as discussed above, that Erickson teaches that down-modulation of FcγRI on macrophages which are known to be major effectors in platelet destruction in ITP could result in reduced platelet destruction and Curnow teaches that monocytes and macrophages that express Fc receptors for IgG (FcgR) (CD64) play an important role in platelet destruction and that crosslinking CD64 by CD64 specific antibodies down modulates CD64 significantly and therefore said antibodies may be useful in treating the autoimmune disease of ITP.

The examiner agrees with applicant that teachings of Uhr, Ghetie, Rybak and Pastan pertain to immunotoxins, however, notes that immunotoxins are routinely used in combination with antibody targeting for the purposes of selective killing of unwanted cells in any number of therapies.

Since the motivation, mechanism of action, and reagents, are taught, often redundantly by the above combination of references, the rejection is maintained and repeated below for applicant's convenience, though applicant's arguments have been carefully considered.

Claims 1-2, 8-12 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curnow, R.T. (Cancer Immunol Immunother. 45:210-215, 1997), Graziano et al (J. Immunol. 155:4996-5002, 1995) and Erickson et al (British Journal of Haematology, 92:718-724, 1996), in view of Uhr et al (U.S. Patent No. 5686072) Ghetie et al (U.S. Patent No. 5578706), Rybak et al (U.S. Patent No. 5840840), Pastan et al (U.S. Patent 5489525), and Bjerke et al (ACTA Derm Venereol (Stockh) 1994; Suppl.186:141-142).

Graziano et al teach as above.

Erickson et al teach as above.

Curnow teaches as above.

Uhr et al teach various ricin A chain-containing anti-CD19 and anti-CD22 immunotoxins to be potentially useful reagents for the clinical treatment of human B cell

leukemias and lymphomas and the use of modified components in immunotoxin, such as Fab' antibody fragments and deglycosylated ricin A chain (dgA), has also been investigated (see entire patent, especially column 4, lines 39-64).

Ghetie et al also teach the toxin moiety of the immunotoxin may be any one of a variety of toxins that are commonly employed in the art include, for example, gelonin and saporin and ricin A chain, and most preferably, deglycosylated ricin A chain, (see entire patent, especially column 7, lines 21-27).

Rybak et al teach the use of an RNase protein (preferably, a mammalian protein) as a toxic moiety in a directed cytotoxin and that some members of the RNase A superfamily: include onconase. Cytotoxic reagents of the present invention comprise a protein and recognition moiety of specific binding with a chosen cell surface marker, (see entire patent, especially column 7, lines 30-36).

Pastan teaches cytotoxic binding proteins of the invention are produced by fusing a cytotoxic domain and antigen binding domain derived from monoclonal antibodies. A variety of cytotoxic molecules are suitable for use as the cytotoxic domain in the immunotoxins described here including Pseudomonas exotoxin A (PE), (see entire patent, especially column 8, lines 10-25).

Bjerke et al teach that highly active psoriatic lesions showed highest reactivity with FcRgI monoclonal antibodies and the number of FCR positive cells decreased in correlation to the improvement following therapy (see entire article, especially the first paragraph of the Results section and the Abstract)

Therefore, it would have been obvious to one of skill in the art at the time the invention was made to have combined the immunotoxin technology taught by Vitetta, Rybak and Pastan which comprises an antibody or antibody fragment thereof that binds to FcgRI as taught by Erickson, Graziano and Curnow linked to a toxin as taught by Vitetta, Rybak and Pastan because said immunotoxin will bind to an FcgRI receptor and kill or reduce the activity of FcRgRI bearing macrophages. Furthermore it would have been obvious to one of skill in the art at the time the invention was made to have used said immunotoxin in treating or preventing a disease characterized by an aberrant activity or number of macrophages, such as psoriasis or ITP as taught by Bjerke et al and Curnow et al., respectively, since reducing the number and or activity of macrophages in a macrophage mediated disease should be effective treatment. Furthermore it would have been obvious to one of skill in the art at the time the invention was made to have used the mabs 22, 32 and 197, since Erickson, Graziano and Curnow teach these monoclonal antibodies can bind the FcgRI at a site which is not bound by an endogenous immunoglobulin, and therefore would not interfere with normal Ig mediated uptake of said macrophages. Furthermore it would have been obvious to one of skill in the art at the time the invention was made to have humanized the mabs 22, 32 and 197, since Graziano et al teach that the humanization of the

monoclonal antibody 22 reduces or eliminates immunogenicity (and would similarly apply to the humanization of monoclonal antibodies 32 and 97) and is an important step in the development of anti-FcgRI-based molecules for the treatment of human diseases. Furthermore it would have been obvious to one of skill in the art at the time the invention was made to have used as the toxin part of the immunotoxin, any one of the toxins Gelonin, Saporin, Exotaxin A, Onconase, and Ricin A, since Vitetta, Rybak and Pastan teach that these toxins would be effective in an immunotoxin.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

9. Applicant traverses the rejection of Claims 1 and 13-17 under 35 U.S.C. 103(a) as being unpatentable over Curnow, R.T. (Cancer Immunol Immunother. 45:210-215, 1997), Graziano et al (J. Immunol. 155:4996-5002, 1995), and Erickson et al (British Journal of Haematology, 92:718-724, 1996), in view of McGrath et al (U.S. Patent No. 5580715), Estis et al (U.S. Patent No. 5026557), Rodwell et al (U.S. Patent 4671958), Lifson et al (U.S. Patent 4869903), and Bagshawe (U.S. Patent 5658568), on the grounds that Curnow, Graziano and Erickson fail to teach or suggest any method of preventing or treating macrophage mediated disorders by selectively targeting macrophages using an Fc receptor binding agent, with which examiner disagrees with as discussed above.

Applicant further contends that McGrath does not make up for this deficiency because while said reference refers to the targeting of macrophages using a liposome based agent, this is carried out using anti-CD14 which is not an agent that binds to an Fc receptor. However examiner notes first that McGrath reference does not have to make up a deficiency which does not exist, and second said reference demonstrates targeting of macrophages with liposomes using a macrophage specific antibody , (though the reference teaches anti-CD14, another antibody directed to macrophages such as an antibody specific for an Fc receptor could be interchanged).

The 103 rejection is not based on hindsight as applicants contend because Curnow et al and Erikson teach treating or preventing a disease characterized by an aberrant activity or number of macrophages, such as ITP, and also teach that reducing the activity of macrophages in said macrophage mediated disease should be effective treatment. The use of the FcI receptor antibody taught by Graziano and the liposome cytotoxic targeting techniques taught by the other refferences which are routine in the art at the time the invention was made, in the methods taught by Curnow et al and Erikson et al would have been obvious to one of skill in the art. Therefore, the rejection is maintained and repeated below for applicant's convenience, though applicant's arguments have been carefully considered.

Claims 1 and 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curnow, R.T. (Cancer Immunol Immunother. 45:210-215, 1997), Graziano et al (J. Immunol. 155:4996-5002, 1995), and Erickson et al (British Journal of Haematology, 92:718-724, 1996), in view of McGrath et al (U.S. Patent No. 5580715), Estis et al (U.S. Patent No. 5026557), Rodwell et al (U.S. Patent 4671958), Lifson et al (U.S. Patent 4869903), and Bagshawe (U.S. Patent 5658568).

Graziano et al teach as above.

Erickson et al teach as above.

Curnow teaches as above.

McGrath et al teaches the following; a method that features a liposome preparation containing within the liposome macrophage-specific cytotoxin or a broad-spectrum cytotoxic agent for the uptake of the cytotoxin-containing liposome preferentially by a macrophage. Targeting of the cytotoxin-containing liposome to a macrophage provides specificity of delivery and increased uptake. Targeting is accomplished by incorporation or attachment of a macrophage-specific antibody such as anti-CD14 to the liposome. Appropriate lipids and other agents and methods for the preparation of therapeutic liposomes are well known in the art, (see entire patent, especially column 6, lines 66-67 and column 6, lines 1-15).

Estis al teach that liposomes carrying CL2MDP, by referring to the reference Claassen, E. et al., "Immunomodulation with Liposomes: the Immune Response Elicited by Liposomes with Entrapped Dichloromethylene-Diphosphonate and Surface-Associated Antigen or Hapten", Immunol., 60:509-515 (1987), (see entire patent, especially column 1).

Rodwell et al teach liposome mediated delivery of pharmaceutical agents and that whether or not liposomes are coated with antibody molecules, liposomes are readily phagocytosed by macrophages and removed from circulation before reaching other target sites, (see entire patent, especially column 19, lines 35-38).

Liffson et al teach that a protein may be administered in a liposome-encapsulated form, and attached to a carrier, such as an anti-T cell, anti-macrophage, or anti-HIV antibody, for targeting the protein to HIV-injectable or infected cells, (see entire patent, especially column 7, lines 32-37).

Bagshawe teaches the advantages of using antibody fragments, rather than

whole antibodies, are several-fold, including the smaller size of the fragments that may lead to improved pharmacological properties, such as better penetration of solid tissue, and effector functions of whole antibodies, such as complement binding, are removed, and Fab, Fv, ScFv antibody fragments can all be expressed in and secreted from E. coli, thus allowing the facile production of large amounts of the said fragments, (see entire patent, especially column 4, lines 1-19).

Therefore, it would have been obvious to one of skill in the art at the time the invention was made to have combined the macrophage binding monoclonal antibody compounds taught by Erickson, Graziano and Curnow within a liposome in the claimed method because said compounds bind macrophages as taught by Erickson, Graziano and Curnow and discussed supra, and because Liffson et al teach that a protein may be administered in a liposome-encapsulated form, and antibodies are proteins and because Rodwell et al teaches that liposomes are readily phagocytosed by macrophages. Furthermore it would have been obvious to one of skill in the art at the time the invention was made to have used a single chain antibody, or fragment thereof of the FcgRI binding monoclonal antibodies taught by Erickson, Graziano and Curnow since Bagshawe teaches the advantages of using antibody fragments including improved pharmacological properties. Furthermore it would have been obvious to one of skill in the art at the time the invention was made to have combined the cytotoxic agent CL2MDP in a liposome in the claimed method because Estis al teach that liposomes can carrying CL2MDP and because McGrath et al teaches a method that features a liposome preparation containing within the liposome macrophage-specific cytotoxin or a broad-spectrum cytotoxic agent for the uptake of the cytotoxin-containing liposome preferentially by a macrophage and that methods for the preparation of therapeutic liposomes are well known in the art .

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. No claim is allowed.

11 Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy DeCloux whose telephone number is (703) 306-5821. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Amy DeCloux, Ph.D.
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March 26, 2001

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